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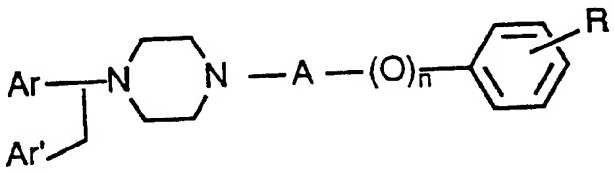
(71) Applicant: **SANTEN PHARMACEUTICAL CO., LTD.**
9-19, Shimoshinjo 3-chome
Higashiyodogawa-ku Osaka-shi Osaka 533(JP)

(72) Inventor: **Morita, Takakazu, 302**
Kitasakurazuka Park Heim
6-8 Kitasakurazuka 3-chome
Toyonaka-shi, Osaka(JP)
Inventor: **Iso, Tadashi**
22-18 Kiyomidai 1-chome
Kawachinagano-Shi, Osaka(JP)
Inventor: **Yamauchi, Hideyasu**
100 Banchi, 1-chome, Umegaoka
Nagaokakyo-Shi, Kyoto(JP)

(74) Representative: **Pearce, Anthony Richmond et al**
MARKS & CLERK Alpha Tower Suffolk Street Queensway Birmingham B1 1TT(GB)

(54) Agent for the treatment of disorders of the cerebral neurotransmitter system.

(57) A therapeutic agent for disorders of cerebro-neural transmission system containing a compound of the formula [I] or salts thereof as an active ingredient,



[I]

wherein
Ar or Ar′ is phenyl or pyridyl, which can be substituted by lower alkyl, lower alkoxy, halogen or lower alkylenedioxy ;
R is hydrogen, lower alkyl, lower alkoxy, halogen or lower alkylenedioxy ;
A is straight or branched alkylene having 1 to 6 carbon atoms ; and
n is 0 or 1; and a method of preparation therefore are disclosed.

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Agent for treatment of disorders of cerebro-neural transmission system.

BACKGROUND OF THE INVENTION

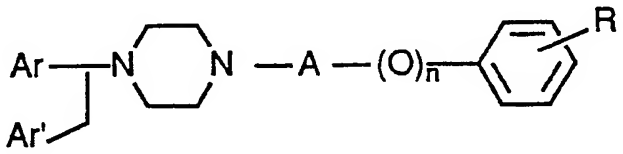
Diphenylethylamine derivatives were well recognized analgesic (Japanese Patent Publication 24084/1961 etc.) and especially (-)-N,N-dimethyl-1,2-diphenylethylamine, lefetamine, is known to have an excellent analgesic effect.

Chemical modification of amine moiety was also studied, and diphenylethylpiperazine derivatives were reported in Japanese Patent Publication 33827/1986 to have an analgesic effect. Furthermore, we reported that diphenylethylpiperazine derivatives had a calcium antagonistic effect (Japanese Unexamined Patent Publication 141966/1988). Diphenylethylpiperazine derivatives were already known to have analgesic effect and calcium antagonistic effect, but the other useful pharmacological properties were not known.

DETAILED DESCRIPTION OF THE INVENTION

This invention relates to :

1) agent, having the chemical formula [I] or salts thereof which includes novel compounds as well as known compounds, for treatment of disorders of cerebro-neural transmission system,



[I]

wherein

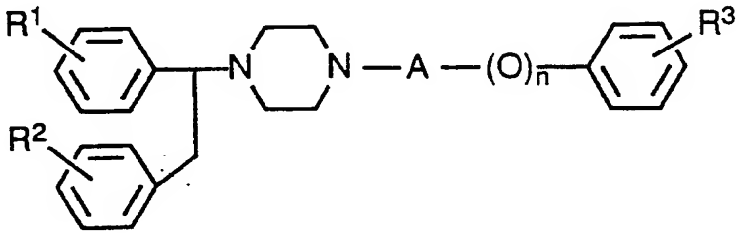
Ar or Ar' is phenyl or pyridyl, which can be substituted by lower alkyl, lower alkoxy, halogen or lower alkylenedioxy ;

R is hydrogen, lower alkyl, lower alkoxy, halogen or lower alkylenedioxy ;

A is straight or branched alkylene having 1 to 6 carbon atoms ; and

n is 0 or 1,

2) novel fluor-compounds of the formula [II] or salts thereof which are useful for treatment of disorders of cerebro-neural transmission system,



[II]

wherein

R^1 is hydrogen or fluorine;

R^2 is hydrogen or fluorine;

R^3 is hydrogen, lower alkyl, lower alkoxy, halogen or lower alkylenedioxy ;

A is straight or branched lower alkylene having 1 to 6 carbon atoms ; and n is 0 or 1,

provided that at least one of R^1 or R^2 is fluorine.

The terms defined above are explained as follows in more detail.

The term "lower alkyl" intends to designate straight or branched alkyl having 1 to 6 carbon atoms exemplified by methyl, ethyl, propyl, isopropyl, butyl and hexyl. The term "lower alkoxy" intends to

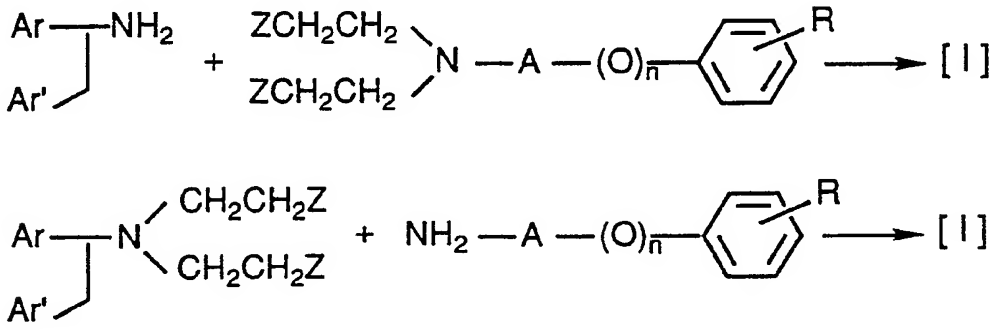
designate straight or branched alkoxy having 1 to 6 carbon atoms exemplified by methoxy, ethoxy, propoxy, isopropoxy, butoxy and hexyloxy. The term "lower alkylenedioxy" intends to designate alkylenedioxy having 1 to 3 carbon atoms exemplified by methylenedioxy and ethylenedioxy. The term "halogen" intends to designate fluorine, chlorine, bromine and iodine. The substituent of phenyl or pyridyl group can be one or more. When the group has plural substituents, the substituents can be the same or different.

The "salt" means a pharmaceutically acceptable salt such as hydrochloric acid salt, sulfuric acid salt, phosphoric acid salt, lactic acid salt, maleic acid salt and oxalic acid salt.

Hereinafter, the compound represented by the formula [I] is referred to as the "Compound" and the compound of the formula [II] is referred to as the "Fluor-Compound".

The Fluor-Compound is a novel compound which has not been disclosed in any prior arts. The definition of the Fluor-Compound is different from that of the Compound, but the Fluor-Compound is included in the scope of the Compound.

Synthetic methods of the Compound are shown below,



wherein Z is hydrogen or methanesulfonyl.

The Compound has optical- or stereoisomer because of the existence of one or more asymmetric carbon atoms, and the isomer is included in this invention.

As mentioned before, piperazine derivatives were known to have analgesic effect and calcium antagonistic effect. We studied the known piperazine derivatives for their new pharmacological effects. Furthermore, we synthesized novel compounds, namely Fluor-Compound, and studied their pharmacological effects.

As the result of our study, we found that the Compound has excellent improvement effect on disorders of cerebro-neural transmission system. Particularly, the Fluor-Compound improved defects of memory very excellently.

As the disorders of cerebro-neural transmission system, many kinds of defect of memory, insomnia, depression, schizophrenia etc. are known. Medicinal substance which improves such disorders is useful for treatment or prevention of senile dementia such as Alzheimer's disease and dementia caused by disorders of cerebral vessel, dementia caused by Parkinson disease or head injuries, etc., insomnia, depression or schizophrenia, etc.

As examples of the studies to examine improvable effects on disorders of cerebro-neural transmission system, one-trial passive avoidance test in mice and antagonistic test against 5-hydroxytryptamine (serotonine, hereinafter referred to as 5-HT) using vessels of rabbits were disclosed. 5-HT has various actions on the central nervous system and the existence of two types of 5-HT receptor, namely type 1 and type 2, was reported (hereinafter type 2 receptor is referred to as 5-HT_2).

It is reported that medical substance showing 5-HT_2 antagonistic effect has improves defect of memory (Pharmacol. Biochem. Behav., 28, 353-359 (1987)), insomnia (Brain Res., 378, 164-168 (1986)), depression (Science, 210, 88-90, (1980)), or psychopathia (J. Pharmacol. Exp. Ther., 228, 133-139, (1984) and J. Pharm. Soc. Jap., 106, 351-370 (1986)).

Therefore, 5-HT_2 antagonist is effective on various kinds of disorders of cerebro-neural transmission system. The Compound showed excellent effect in the above mentioned tests. The details are explained in the part of pharmacological test.

Especially, the Fluor-Compound, even in a low dosage, showed an excellent effect in the one-trial passive avoidance test with higher efficacy than the known compounds. This suggests that the Fluor-Compound would be useful for treatment of dementia.

The Compound can be administered either orally or parenterally. Examples of the dosage forms are

tablet, capsule, granules, powder, suppository and injection. The dosage is adjusted depending on symptom, dosage form, etc., but usual daily dosage is 1 to 1000mg in one or a few divided doses.

PHARMACOLOGICAL TEST

As examples of pharmacological tests, one-trial passive avoidance test in mice (pharmacological test 1) and antagonistic test against 5-HT_2 using vessel of rabbit (pharmacological test 2) were shown.

Novel Fluor-Compound, which has not been disclosed in any prior arts, and the known compounds disclosed in Japanese Unexamined Patent Publication 141966/1988 and optical isomers thereof were tested. Examples of the compounds tested are shown as below.

(±)-1-[1,2-Bis(4-fluorophenyl)]ethyl-4-[2-(3,4-dimethoxyphenyl)ethyl]piperazine dihydrochloride (compound No.1)
mp 265 - 267 °C (dec.)
(±)-1-[1-(4-Fluorophenyl)-2-phenyl]ethyl-4-[2-(3,4-dimethoxyphenyl)ethyl]piperazine dihydrochloride (compound No.2)
mp 263 °C (dec.)
(±)-1-[2-(4-Fluorophenyl)-1-phenyl]ethyl-4-[2-(3,4-dimethoxyphenyl)ethyl]piperazine dihydrochloride (compound No.3)
mp 264 °C (dec.)
(±)-1-(1,2-Diphenyl)ethyl-4-[2-(3,4-dimethoxyphenyl)ethyl]piperazine dihydrochloride (compound No.4)
mp 251 - 254 °C (dec.)
(-)-1-(1,2-Diphenyl)ethyl-4-[2-(3,4-dimethoxyphenyl)ethyl]piperazine dihydrochloride (compound No.5)
mp 225 - 230 °C (dec.)
(+)-1-(1,2-Diphenyl)ethyl-4-[2-(3,4-dimethoxyphenyl)ethyl]piperazine dihydrochloride (compound No.6)
mp 225 - 230 °C (dec.)
(±)-1-(1,2-Diphenyl)ethyl-4-[2-(3,4-methylenedioxyphenoxy)ethyl]piperazine dihydrochloride (compound No.7)
mp 242 - 243 °C (dec.)
(±)-1-[2-Phenyl-1-(4-pyridyl)ethyl]-4-[2-(3,4-dimethoxyphenyl)ethyl]piperazine dioxalate (compound No.8)
mp 168 - 171 °C (dec.)
(±)-1-[(2-Phenyl)-1-(3-pyridyl)ethyl]-4-[2-(3,4-methylenedioxy phenoxy)ethyl]piperazine dioxalate (compound No.9)
mp 172 - 175 °C (dec.)
(±)-1-[1,2-Bis(4-fluorophenyl)]ethyl-4-[2-[(3,4-methylenedioxy)phenoxy]ethyl]piperazine dihydrochloride (compound No.10)
mp 246 - 247 °C (dec.)
(-)-1-[1,2-Bis(4-fluorophenyl)]ethyl-4-[2-(3,4-dimethoxyphenyl)ethyl]piperazine dihydrochloride (compound No.11)
mp 266 - 267 °C (dec.)
(+)-1-[1,2-Bis(4-fluorophenyl)]ethyl-4-[2-(3,4-dimethoxyphenyl)ethyl]piperazine dihydrochloride (compound No.12)
mp 266 - 267 °C (dec.)

Pharmacological Test 1

As an experimental method to examine an efficacy of a medicinal substance on dementia, one-trial passive avoidance test is well known (Jarvic and Essman, Psychol. Rep., 6,290 (1960)).

(Experimental Method)

In the training session, each mouse was gently placed onto the wooden platform (4 x 4 x 4cm) set in the center of the grid floor (21 x 21cm). When the mouse stepped down from the platform and placed all its paws on the grid floor, the intermittent electric shocks (1Hz, 0.5sec, 60 VDC) were delivered. The step-down latency was measured, and the animals exhibiting a step-down latency ranging from 3 to 15sec were

used for the retention test.

Twenty-four hours after training, each mouse was placed on the platform again, and the step-down latency was recorded up to a maximum cut off time of 300sec.

Impairment of memory was induced by cycloheximide (CXM, protein synthesis inhibitor) or p-chloramphetamine (PCA, a release of 5-HT). CXM (60mg/kg) dissolved in 0.9% saline was injected s.c. immediately after training session. On the other hand, PCA (5mg/kg) dissolved in 0.9% saline was injected i.p. 30min before training session. The test compound was suspended in 1.0% methylcellulose and administered p.o. immediately after training session.

Normal mice were given 0.9% saline (s.c. or i.p.) and 1.0% methylcellulose (p.o.) in a volume of 0.1ml/10g body weight.

Control mice were given CXM or PCA alone.

(Result)

The experimental results are shown in Table 1 and 2.

Table 1

PCA - induced amnesia model		
	dose(mg/kg)	step-down latency (median, sec.)
normal		250.7
control		160.1
compound No.1	1.25	263.6
normal		176.1
control		18.6
compound No.1	10.0	130.1
normal		271.8
control		52.7
compound No.2	2.5	199,9
normal		271.8
control		52.7
compound No.3	2.5	198.2
normal		176.1
control		18.6
compound No.4	10.0	184.7
normal		203.1
control		35.0
compound No.7	5.0	155.1
normal		203.1
control		35.0
compound No.10	1.25	206.3
normal		165.1
control		43.6
compound No.11	2.5	153.1
normal		165.1
control		43.6
compound No.12	2.5	132.0

Table 2

CXM - induced amnesia model		
	dose(mg/kg)	step-down latency (median, sec.)
normal		225.4
control		25.3
compound No.4	40.0	77.7
normal		300.0
control		21.9
compound No.5	20.0	60.0
normal		224.1
control		23.6
compound No.6	20.0	115.4
normal		215.6
control		32.5
compound No.7	20.0	123.9

As shown in the tables, the reduction of step-down latency in control group was improved by all the compounds tested. Particularly, the group receiving the Fluor-Compound recovered its latency time to the same level or almost same level to the normal group. Furthermore, the Fluor-Compound showed very high efficacy at low doses, namely 1.25 or 2.5 mg/kg.

The result proved that the Compound can be useful for treatment of dementia.

Pharmacological Test 2

It is reported that a medicinal substance having 5-HT_2 antagonistic effect improves various kinds of cerebro-neural transmission system. The effect comes from the action of such substance on 5-HT_2 receptor in brain. It is reported that 5-HT_2 antagonistic effect of the medical substance on smooth muscle of vessel is correlating to the binding ability with 5-HT_2 receptor in brain (Leysen, J. E. et al., Molecular Pharmacology, 21, 301 - 314 (1982)). Therefore, in this test, the efficacy of the Compound was examined using thoracic aorta of rabbit.

(Experimental Method)

Japanese white rabbits were sacrificed by cervical fracture and exsanguinated. Thoracic aortas were excised rapidly. The isolated arteries were helically cut into strips, approximately 3mm wide, and suspended in 20ml organ bath chambers containing Krebs-Henseleit solution. Resting tensions of aortas were maintained at 1.5g. The organ bath chambers were maintained at 37° C and aerated continuously with 95% O_2 - 5% CO_2.

After equilibration, 5-HT (10^{-6}M) was added into each organ bath chamber. After the 5-HT-induced contraction was ascertained to be constant and reproducible, each test compound were added and 30min after 5-HT was added again, and their effect on 5-HT-induced contraction was examined.

The contraction was measured with various concentrations of the test compound. According to the difference between the contraction caused by pre-treatment with the test compound and by 5-HT alone, the concentration which can inhibit 50% of the contraction caused by 5-HT alone was calculated (IC_{50}).

Result

The experimental results were shown in the Table 3.

Table 3

test compound (compound No.)	IC_{50} (M)
1	2.7×10^{-7}
2	3.4×10^{-7}
3	6.4×10^{-7}
4	2.8×10^{-7}
5	2.1×10^{-7}
6	2.0×10^{-6}
7	2.7×10^{-6}
8	7.0×10^{-6}
9	4.8×10^{-6}
10	2.1×10^{-6}
11	2.0×10^{-7}

As shown in the table, the Compound shows excellent inhibition of the contraction caused by 5-HT. The results confirms the excellent 5-HT_2 antagonistic effect of the Compound because the contraction of smooth muscle of vessel is relating to 5-HT_2 receptor.

EXAMPLE

Synthesis of novel Fluor-Compound are shown below.

(Preparation of the intermediate)

1. N,N-Bis(2-chloroethyl)-2-(3,4-dimethoxyphenyl)ethylamine hydrochloride

2-(3,4-Dimethoxyphenyl)ethylamine (80.0g), 2-bromoethanol (182g) and potassium carbonate (201g) were added to ethanol (1 ℓ) and the mixture was refluxed for 16 hours. After cooling, the mixture was filtered and the filtrate was concentrated in vacuo. The oily residue was dissolved in chloroform. The solution was washed with saturated sodium chloride solution, dried over anhydrous magnesium sulfate and concentrated in vacuo to give 104.5g(88%) of N,N-bis(2-hydroxyethyl)-2-(3,4-dimethoxyphenyl)ethylamine in oily form.

The amine compound (104g) was dissolved in chloroform (500ml). To the solution, thionyl chloride (138g) was added dropwise under ice-cooling. After the addition, the reaction mixture was refluxed for 45 minutes with stirring. After cooling, the reaction mixture was concentrated in vacuo. To the oily residue, isopropanol was added and separated crystals were collected by filtration to give 88.9g (67.2%) of the titled compound.

mp 145 - 148 °C (dec.)

IR (KBr, cm^{-1}) 2920, 2380, 1590, 1509, 1450, 1262, 1237, 1158, 1139, 1025, 979

Following compound was prepared by the similar method as in the above.

N,N-Bis(2-chloroethyl)-2-[(3,4-methylenedioxy)phenoxy]ethylamine hydrochloride

IR (film, cm^{-1}) 3376, 2972, 2388, 1609, 1488, 1270, 1184, 1130, 1038, 952, 817

2. (±)-1,2-Bis(4-fluorophenyl)ethylamine hydrochloride

A mixture of 1,2-bis(4-fluorophenyl)-1-oxoethane (2.13g) and ammonium formate (3.78g) was stirred for 10 hours at 190 °C. After cooling, concentrated hydrochloric acid (12ml) was added to the reaction mixture and the mixture was refluxed for 5 hours. After cooling, aqueous sodium hydroxide solution was added to the mixture and alkalized. The product was extracted with ethyl acetate and the organic layer was washed with saturated sodium chloride solution. The organic layer was dried over anhydrous magnesium sulfate and concentrated in vacuo. The oily residue was dissolved in methanol. To the solution, HCl/methanol was added and the solution was concentrated in vacuo. Separated crystals were collected by filtration to give 1.77g (65.6%) of the titled compound.

mp 238 - 240 °C (ethanol - ether)

IR (KBr, cm^{-1}) 3384, 2924, 1601, 1508, 1438, 1258, 1229, 1154, 1020, 835, 820

Following compounds were prepared by the similar method as in the above.

(±)-1-(4-Fluorophenyl)-2-phenylethylamine hydrochloride

mp 266 - 268 °C (methanol - ether)

IR (KBr, cm^{-1}) 3480, 2860, 1605, 1515, 1233, 835, 749, 697

(±)-2-(4-Fluorophenyl)-1-phenylethylamine hydrochloride

mp 257 - 259 °C (dec.), (methanol - ether)

IR (KBr, cm^{-1}) 3412, 2892, 1600, 1512, 1227, 835, 699

3. (-)-1,2-Bis(4-fluorophenyl)ethylamine 1/2(+)-tartrate (1) and (+)-1,2-Bis(4-fluorophenyl)ethylamine 1/2(-)-tartrate (2)

To (±) 1,2-bis(4-fluorophenyl)ethylamine (4.67g, prepared by treatment of the hydrochloric acid salt with potassium carbonate) dissolved in ethanol (20ml), (+)-tartaric acid (1.50g) was added and the mixture was warmed to be solution. Water (200ml) was added to the solution and the mixture was warmed again to be homogeneous solution. The solution was stirred for one night at room temperature and separated crystals were collected by filtration. The crude crystals were recrystallized with water to give 1.12g (36%) of the titled compound(1).

mp 221 - 222 °C (dec.), (water)

IR (KBr, cm^{-1}) 3424, 2896, 1608, 1560, 1511, 1344, 1228, 1067, 845, 819

$[\alpha]_D^{25}$ -66.3 ° (c = 1.0, methanol)

To the filtrate removed the crude crystals of the titled compound(1), potassium carbonate was added and alkalized. From the mixture, (+)-rich amine compound (2.40g) was obtained by extraction with ethyl acetate. (-)-Tartaric acid (0.75g) was added to ethanol (10ml) solution of (+)-rich amine compound and the mixture was warmed to be solution. Water(100ml) was added to the solution and the mixture was stirred for one night at room temperature and separated crystals were collected by filtration to give 1.27g (41%) of the titled compound(2).

mp 223 °C (dec.),(water)

IR (KBr, cm^{-1}) 3424, 2892, 1608, 1559, 1510, 1345, 1228, 1607, 845, 819

$[\alpha]_D^{25}$ +69.3 ° (c = 1.0, methanol)

Following compounds were prepared by the similar method as in the above.

(-)-1-(4-Fluorophenyl)-2-phenylethylamine 1/2(+)-tartrate

mp 223 °C (dec.), (water)

IR (KBr, cm^{-1}) 3424, 2892, 1608, 1559, 1516, 1343, 1225, 1067, 845, 748, 694

$[\alpha]_D^{25}$ -68.1 (c = 0.3, methanol)

(+)-1-(4-Fluorophenyl)-2-phenylethylamine 1/2(-)-tartrate

mp 221 - 222 °C (dec.), (water)

IR (KBr, cm^{-1}) 3424, 2892, 1606, 1557, 1515, 1343, 1226, 1068, 846, 748, 694

$[\alpha]_D^{25}$ +65.5 ° (c = 0.3, methanol)

(-)-2-(4-Fluorophenyl)-1-phenylethylamine 1/2(+)-tartrate

mp 213 °C (dec.), (water)

IR (KBr, cm^{-1}) 3432, 2900, 1599, 1566, 1512, 1345, 1234, 1067, 825, 701

$[\alpha]_D^{25}$ -66.9 ° (c = 0.3, methanol)

(+)-2-(4-Fluorophenyl)-1-phenylethylamine 1/2(-)-tartrate

mp 211 - 213 °C (dec.), (water)

IR (KBr, cm^{-1}) 3432, 2892, 1597, 1564, 1511, 1344, 1233, 1066, 824, 700

$[\alpha]_D^{25}$ +69.7 ° (c=0.3, methanol)

Example 1

(±)-1-[1,2-Bis(4-fluorophenyl)]ethyl-4-[2-(3,4-dimethoxyphenyl)ethyl]piperazine dihydrochloride (compound No.1)

(±)-1,2-Bis(4-fluorophenyl)ethylamine (750mg, prepared by treatment of the hydrochloric acid salt with potassium carbonate), N,N-bis(2-chloroethyl)-2-(3,4-dimethoxyphenyl)ethylamine hydrochloride (738mg), sodium iodide (965mg) and potassium carbonate (445mg) were added to N,N-dimethylformamide (DMF, 18ml) and the mixture was stirred for 2 hours at 80 ° C. The reaction mixture was poured into water (150ml) and extracted with ethyl acetate. The organic layer was washed with saturated sodium chloride solution, dried over anhydrous magnesium sulfate and concentrated in vacuo. The oily residue was purified by silica gel column chromatography. The purified oily product was dissolved in methanol. To the solution, HCl/methanol was added and the solution was concentrated in vacuo. Separated crystals were collected by filtration to give 670mg (57.9%) of the titled compound.
mp 265 - 267 ° C (dec.), (methanol - ethanol - ethyl acetate)
IR (KBr, cm^{-1}) 3368, 2920, 2296, 1601, 1508, 1437, 1258, 1229, 1152, 1019, 835
Following compounds were prepared by the similar method as in the above.
(±)-1-[1-(4-Fluorophenyl)-2-phenyl]ethyl-4-[2-(3,4-dimethoxyphenyl)ethyl]piperazine dihydrochloride (compound No.2)
mp 263 ° C (dec.), (ethanol)
IR (KBr, cm^{-1}) 3408, 2980, 2320, 1604, 1515, 1451, 1257, 1147, 1025, 843
(±)-1-[2-(4-Fluorophenyl)-1-phenyl]ethyl-4-[2-(3,4-dimethoxyphenyl)ethyl]piperazine dihydrochloride (compound No.3)
mp 264 ° C (dec.), (ethanol)
IR (KBr, cm^{-1}) 3412, 2936, 2320, 1602, 1509, 1453, 1260, 1156, 1023, 759
(±)-1-[1,2-Bis(4-fluorophenyl)]ethyl-4-[2-[(3,4-methylenedioxy) phenoxy]ethyl]piperazine dihydrochloride (compound No.10)
mp 246 - 247 ° C (dec.), (ethanol)
IR (KBr, cm^{-1}) 3416, 2984, 2324, 1606, 1509, 1489, 1230, 1184, 1035, 841

Example 2

(-)-1-[1,2-Bis(4-fluorophenyl)]ethyl-4-[2-(3,4-dimethoxyphenyl)ethyl]piperazine dihydrochloride (compound No.11)

To a solution of (-)-1,2-bis(4-fluorophenyl)ethylamine 1/2(+)-tartrate (950mg) and N,N-bis(2-chloroethyl)-2-(3,4-dimethoxyphenyl)ethylamine hydrochloride (754mg) in DMF (40ml), sodium iodide (989mg) and potassium carbonate (1764mg) were added and the mixture was stirred for 2 hours at 80 ° C. After cooling, ethyl acetate and water were added to the mixture. The organic layer was washed with water and saturated sodium chloride solution, dried over anhydrous magnesium sulfate and concentrated in vacuo. To the oily product dissolved in ethanol, HCl/ methanol was added and separated crystals were collected by filtration to give 597mg (50%) of the titled compound.
mp 266 - 267 ° C (dec.), (ethanol)
IR (KBr, cm^{-1}) 3420, 2940, 2324, 1606, 1515, 1452, 1259, 1150, 1025, 841
$[\alpha]_D^{25}$ -34.2 ° (c=0.2, methanol)
Following compounds were prepared by the similar method as in the above.
(+)-1-[1,2-Bis(4-fluorophenyl)]ethyl-4-[2-(3,4-dimethoxyphenyl)ethyl]piperazine dihydrochloride (compound No.12)
mp 266 - 267 ° C (dec.), (ethanol)
IR (KBr, cm^{-1}) 3424, 2980, 2316, 1606, 1510, 1452, 1258, 1148, 1025, 841
$[\alpha]_D^{25}$ +34.0 ° (c=0.2, methanol)
(-)-1-[1-(4-Fluorophenyl)-2-phenyl]ethyl-4-[2-(3,4-dimethoxyphenyl)ethyl]piperazine dihydrochloride

(compound No.13)
mp 265 - 266 °C (dec.), (ethanol)
IR(KBr, cm^{-1}) 3412, 2984, 2324, 1605, 1517, 1451, 1258, 1148, 1026, 843
$[\alpha]_D^{25}$ -37.2 ° (c=0.3, methanol)
(+)-1-[1-(4-Fluorophenyl)-2-phenyl]ethyl-4-[2-(3,4-dimethoxyphenyl)ethyl]piperazine dihydrochloride
(compound No.14)
mp 265 - 266 °C (dec.), (ethanol)
IR (KBr, cm^{-1}) 3416, 2984, 2336, 1606, 1518, 1452, 1258, 1148, 1026, 844
$[\alpha]_D^{25}$ +39.7 ° (c=0.3, methanol)
(-)-1-[2-(4-Fluorophenyl)-1-phenyl]ethyl-4-[2-(3,4-dimethoxyphenyl)ethyl]piperazine dihydrochloride
(compound No.15)
mp 265 - 266 °C (dec.), (ethanol)
IR (KBr, cm^{-1}) 3424, 2948, 2324, 1593, 1509, 1450, 1260, 1146, 1030, 761
$[\alpha]_D^{25}$ -38.7 ° (c=0.3, methanol)
(+)-1-[2-(4-Fluorophenyl)-1-phenyl]ethyl-4-[2-(3,4-dimethoxyphenyl)ethyl]piperazine dihydrochloride
(compound No.16)
mp 264 - 266 °C (dec.), (ethanol)
IR (KBr, cm^{-1}) 3428, 2944, 2320, 1593, 1512, 1451, 1260, 1145, 1028, 761
$[\alpha]_D^{25}$ + 36.8 ° (c=0.3, methanol)

FORMULATIONS

The following formulations are illustrative.

A) Tablet	
compound No.1	5mg
lactose	74.4mg
starch	20mg
hydroxypropylcellulose	4mg
calcium carboxymethylcellulose	6mg
magnesium stearate	0.6mg
total	110mg

compound No.1	30mg
lactose	49.4mg
starch	20mg
hydroxypropylcellulose	4mg
calcium carboxymethylcellulose	6mg
magnesium stearate	0.6mg
total	110mg

compound No.2	10mg
lactose	78mg
crystalline cellulose	25mg
low substituted hydroxypropylcellulose	6mg
magnesium stearate	1mg
total	120mg

compound No.3	50mg
lactose	68mg
crystalline cellulose	40mg
low substituted hydroxypropylcellulose	10mg
magnesium stearate	2mg
total	170mg

compound No.4	10mg
lactose	100mg
crystalline cellulose	40mg
hydroxypropylcellulose	8mg
low substituted hydroxypropylcellulose	10mg
magnesium stearate	2mg
total	170mg

B) Granule	
compound No.4	30mg
lactose	145mg
polyvinyl pyrrolidone	15mg
calcium carboxymethylcellulose	5mg
magnesium stearate	5mg
total	200mg

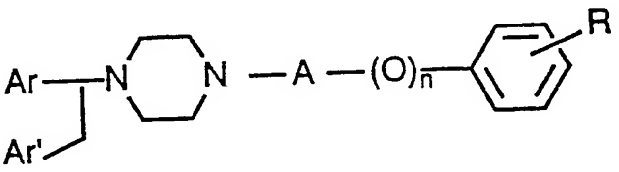
compound No.11	30mg
lactose	145mg
polyvinyl pyrrolidone	15mg
calcium carboxymethylcellulose	5mg
magnesium stearate	5mg
total	200mg

C) Capsule	
compound No.4	5mg
lactose	140mg
magnesium stearate	5mg
total	150mg

compound No.12	30mg
lactose	145mg
polyvinyl pyrrolidone	15mg
calcium carboxymethylcellulose	5mg
magnesium stearate	5mg
total	200mg

Claims

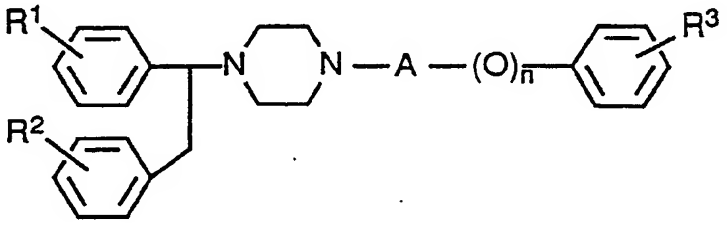
1. A therapeutic agent for disorders of cerebro-neural transmission system containing a compound of the formula [1] or salts thereof as an active ingredient,



[I]

wherein
Ar or Ar' is phenyl or pyridyl, which can be substituted by lower alkyl, lower alkoxy, halogen or lower alkylenedioxy ;
R is hydrogen, lower alkyl, lower alkoxy, halogen or lower alkylenedioxy ;
A is straight or branched alkylene having 1 to 6 carbon atoms ; and
n is 0 or 1.

2. A compound of the formula [II] or salts thereof,



[II]

wherein
R^1 is hydrogen or fluorine;
R^2 is hydrogen or fluorine;
R^3 is hydrogen, lower alkyl, lower alkoxy, halogen or lower alkylenedioxy ;
A is straight or branched lower alkylene having 1 to 6 carbon atoms ; and n is 0 or 1,
provided that at least one of R^1 or R^2 is fluorine.

3. The compound as in claim 2 wherein
R^1 and R^2 are fluorine; and
R^3 is methoxy or methylenedioxy.

4. The compound as in claim 2 wherein
R^1 is hydrogen;
R^2 is fluorine; and
R^3 is methoxy.

5. The compound as in claim 2 wherein
R^1 is fluorine;

R^2 is hydrogen; and
R^3 is methoxy.

6.1-[1,2-Bis(4-fluorophenyl)]ethyl-4-[2-(3,4-dimethoxyphenyl) ethyl]piperazine or salts thereof.

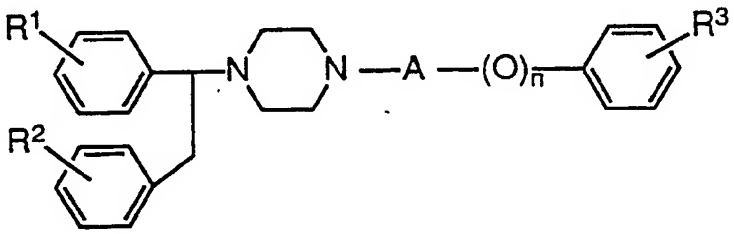
7. 1-[1-(4-Fluorophenyl)-2-phenyl]ethyl-4-[2-(3,4-dimethoxyphenyl)ethyl]piperazine or salts thereof.

8. 1-[2-(4-Fluorophenyl)-1-phenyl]ethyl-4-[2-(3,4-dimethoxyphenyl)ethyl]piperazine or salts thereof.

9. 1-[1,2-Bis(4-fluorophenyl)]ethyl-4-[2-(3,4-methylenedioxy)phenoxy]ethyl]piperazine or salts thereof.

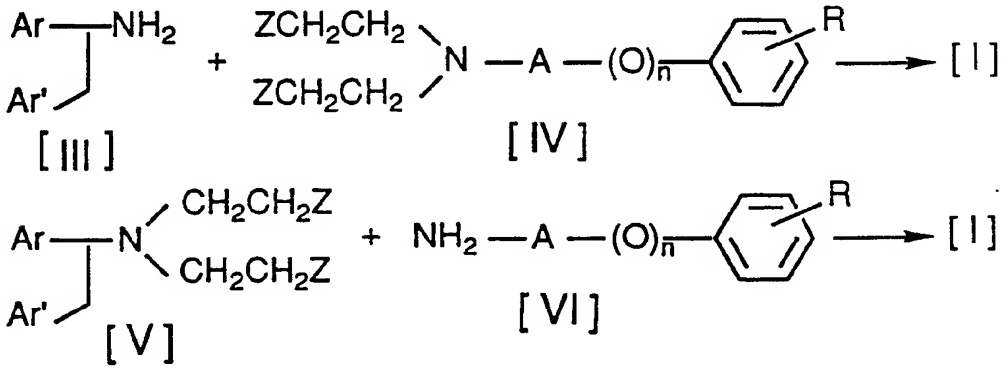
10. The therapeutic agent as in claim 1 wherein the compound is selected from 1-(1,2-diphenyl)ethyl-4-[2-(3,4-dimethoxyphenyl)ethyl]piperazine, 1-[1,2-bis(4-fluorophenyl)]ethyl-4-[2-(3,4-dimethoxyphenyl)ethyl]-piperazine, 1- [1-(4-fluorophenyl)-2-phenyl]ethyl-4-[2-(3,4-dimethoxyphenyl)ethyl]piperazine, 1-[2-(4-fluorophenyl)-1-phenyl]ethyl-4-[2-(3,4-dimethoxyphenyl)ethyl]piperazine , 1-[1,2-bis(4-fluorophenyl)]ethyl-4-[2-(3,4-methylenedioxy)phenoxy]ethyl]piperazine .

11. A process for preparing a compound of the formula [II] or salts thereof,



[II]

wherein
R^1 is hydrogen or fluorine;
R^2 is hydrogen or fluorine;
R^3 is hydrogen, lower alkyl, lower alkoxy, halogen or lower alkylenedioxy ;
A is straight or branched lower alkylene having 1 to 6 carbon atoms ; and n is 0 or 1,
provided that at least one of R^1 or R^2 is fluorine.
which comprises a condensation of a compound of the formula [III] with a compound of the formula [IV] or a condensation of a compound of the formula [V] with a compound of the formula [VI],



[III] [IV] [I]

[V] [VI] [I]

wherein
Z is hydrogen or methanesulfonyloxy.

12. The use of an agent as claimed in any one of claims 1 to 10 for the manufacture of a medicament for the treatment of disorders of the cerebro-neural transmission system.